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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,424	04/11/2001	Carlo M. Croce	8666-009	9552

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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/832,424	Croce et al.
Examiner	**Art Unit**
Michael C. Wilson	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 8, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above, claim(s) *1, 10-12, 14, 16, 18, 20, and 22* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-9, 13, 15, 17, 19, and 21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group II in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the search required for Group I is required for the search of Group II. This is not found persuasive because the restriction is based on the burden required to search and examine the Groups together. The mammal of Group II has considerations regarding enablement, written description and art not required for the mammal of Group I because it has a different mode of operation, different phenotype and different structure. As such, the restriction requirement is deemed proper and is therefore made FINAL.

Claims 1, 10-12, 14, 16, 18, 20 and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 2-9, 13, 15, 17, 19 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a heterozygous disruption in FHIT, wherein said disruption causes increased induction of tumor

formation, does not reasonably provide enablement for any non-human mammal, any transgenic without a phenotype that differs from the wild-type or mice with a homozygous disruption in FHIT. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification does not enable making the transgenic claimed in any species other than mice. Claims 2 and 3 encompass any non-human mammal. The species-specific requirements for transgene design were not clearly understood in the art at the time of filing. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (1990) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al. (1990) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. The specification only teaches making transgenic mice (pg 44) and does not teach the FHIT sequence in any other species or ES cells in species other than mice. The specification does not correlate the mice to any other species such that the sensitivity

to tumor formation obtained in mice could be obtained in other species. Without such guidance it would require one of skill in the art undue experimentation to overcome the unpredictability in the art regarding obtaining the same phenotype in different species and determine how to obtain the transgenic having increased tumor formation in any species other than mice.

The specification does not enable a transgenic without a phenotype as broadly claimed. Claims 2-7, 13, 15, 17, 19 and 21 encompass transgenics having any phenotype including wild-type. Wall (1996, Theriogenology, Vol. 45, pages 57-68) disclosed the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Ebert (1988, Mol. Endocrinology, Vol. 2, pages 277-283) taught a transgene encoding the human somatotropin gene operably linked to the mouse metallothionein promoter caused different phenotypes in transgenic pigs and mice (page 277, column 2, lines 17-27). Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) teach that non-mouse ES cells capable of providing germline chimeras were not available (page S38, column 1, first paragraph). Therefore, it was unpredictable at the time of filing what gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, site of integration, method used and phenotype obtained were required to make a transgenic non-human mammal of

interest. The purpose of the transgenic taught in the specification is to obtain a tumor model for Muir-Torre Syndrome (MTS) which is characterized by a predisposition for developing a combination of sebaceous and visceral tumors (pg 2, line 5). The specification does not provide an enabled use for the transgenic without a predisposition for developing tumors. Claim 8 requires the mouse is "characterized by a predisposition to developing a spectrum of visceral and skin tumors." "Skin tumors" do not correlate with "sebaceous tumors" as described in the specification because "skin" is broader scope than "sebaceous" and "skin tumors" do not accurately reflect the human condition of MTS. Therefore, claim 8 should be limited to visceral and sebaceous tumors. Claim 9 requires the mouse is "characterized by hypersensitivity to NMBA." The specification only teaches the FHIT +/- mice having increased tumor formation upon being exposed to NMBA as compared to FHIT +/+. The specification does not define hypersensitivity to NMBA and the claim does not state to the sensitivity is being compared. In conclusion, the claims should be limited to obtaining increased induction of tumor formation.

The specification does not enable transgenics having a homozygous FHIT disruption. Claims 2-5, 7-9, 13, 15, 17, 19 and 21 encompass transgenics having a homozygous FHIT disruption. Claim 6 is directed toward a transgenic having a homozygous FHIT disruption. The unpredictability in the art regarding the genotype causing the desired phenotype is discussed above. While the specification teaches obtaining FHIT -/- mice that do not express FHIT (pg 44, line 27), the specification does not teach the phenotype of the mice. While the specification teaches FHIT +/- mice have increased susceptibility to tumors, the specification does not compare

FHIT +/- to FHIT -/- mice. Without such guidance the specification does not provide adequate guidance for one of skill in the art to overcome the unpredictability in the art to be able to determine how to use FHIT -/- mice or to predict the phenotype of the FHIT -/- mice.

The specification does not enable a transgenic that merely has cells that contain a disruption of the FHIT locus as claimed. The specification is directed toward altering the genome of the transgenics. As written, the claims encompass injecting cells having a disruption in FHIT into an animal which is not described in the specification. The claims should reflect the invention which must alter the genome of the animal by the hand of man.

The comparison step in the method claims does not enable one of skill to determine which molecules are carcinogenic. The increased rate of tumor formation following administration of the test molecule must be compared to an animal that did not receive the test molecule to determine that the molecule is carcinogen. The comparison is essential to determining carcinogens and should be included in the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 2-9, 13, 15, 17, 19 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "locus" in the claims is indefinite. "Locus" is a position in a chromosome. A disruption in a position does not make sense. The disruption is in the nucleic acid sequence or the FHIT gene.

"An exon 5 coding region" does not make sense. There is only ever one exon 5 in a gene; therefore, the phrase should be "the exon 5 coding region."

The phrase "being characterized by a predisposition to developing a spectrum of visceral and skin tumors" is unclear. "Predisposition" is misspelled. The metes and bounds of a "spectrum" cannot be determined. How wide is the spectrum? The metes and bounds of "characterized" cannot be determined. Do they have the predisposition or do they have something similar to the predisposition? The phenotype of the animal should be clearly set forth.

The phrase "being characterized by a hypersensitivity to NMBA." The metes and bounds of a "hyper" sensitivity cannot be determined. How high is the sensitivity? The metes and bounds of "characterized" cannot be determined. Do they have the hypersensitivity or do they have something similar to the hypersensitivity? The phenotype of the animal should be clearly set forth.

The phrase "wherein an increased rate of tumor formation following administration of the test molecule is indicative" is incomplete because it lacks the essential element of comparing to a control. The increased rate can only be determined when compared to a control that did not receive the test compound.

The phrase "wherein a reduced rate of tumor formation following administration of the test molecule is indicative" is incomplete because it lacks the essential element of comparing to a

control. The reduced rate can only be determined when compared to a control that did not receive the test compound.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 2-5, 7, 13, 15, 17, 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (Scientific American, Vol. 270, 1994, pages 34-41) in view of Julius (US Patent 5,698,766) in view of Pekarsky (1998, Cancer Res., Vol. 58, pg 3409-3414).

Capecchi taught making a HoxA-3 knockout mouse, a mouse model for DiGeorge syndrome (pg 41, col. 1, 3rd full paragraph). Capecchi did not teach disrupting the FHIT gene.

However, Pekarsky taught the nucleic acid sequence of the mouse FHIT gene and that the FHIT protein is lost in many cancer cells due to disruptions in the FHIT gene (see entire article).

Thus it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a transgenic mouse having an disruption in a gene as taught by Capecchi wherein the gene was the FHIT gene taught by Pekarsky. One of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the FHIT in a

transgenic mouse to determine the function of FHIT *in vivo*. Capecchi provides motivation by stating other diseases can be studied by transgenesis (pg 41, col. 2, 2nd full para.) and that mouse models provide an understanding of the gene and make it possible to determine drugs that effect gene regulation (pg 41, col. 2, 2nd full para.).

The combined teachings of Capecchi did not teach inserting stop codons into exon 5 of the FHIT gene.

However, Julius taught a transgenic mouse having a disruption in exon 5 of the 5HT-2C receptor gene. The disruptions were made by inserting stop codons into exon 5 (col. 11-12, Examples 1 and 2; see col. 11, line 55).

Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the FHIT gene as taught by Capecchi and Pekarsy wherein the disruption was caused by inserting stop codons into exon 5 as taught by Julius. One of ordinary skill in the art at the time the invention was made would have been motivated to disrupt the FHIT gene at exon 5 because Pekarsky taught exon 5 was the beginning of the coding region of the FHIT. Therefore, one would have been motivated to disrupt exon 5 of the FHIT gene to completely prevent expression of FHIT.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER